Derived GFR (dGFR) Values from Technetium-99m-MAG3 Data: A Comparison with the 24-Hour Creatinine Clearance

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Objective: Glomerular filtration can eliminate a substance only from the filtered fraction of the renal plasma flow. Since that fraction normally is 20%, ERPF agents clear from the kidneys about five times as fast as GFR agents. In most chronic renal diseases, the filtration fraction (GFR divided by ERPF) is largely unaffected, so the GFR can be estimated by dividing the ERPF by five. The aim of this study was to test this hypothesis.

Methods: ERPF determinations were made in 52 patients. The results were then divided by five to derive GFR values. Each patient had a 24-hr creatinine clearance test within three days of the ^{99m}Tc MAG3 study. Patients with acute renal failure or transplant rejection were excluded from the protocol.

Results: There was a high degree of correlation between the 24-hr creatinine clearance and the derived GFR values (dGFR) obtained from the ^{99m}Tc MAG3 data, $r = 0.97$, $p < 0.05$.

Conclusion: Reliable dGFR values can be easily calculated in most chronic renal states using ^{99m}Tc MAG3 data; these derived values are well correlated to those obtained by the 24-hr creatinine clearance.

Key Words: technetium-99m-MAG3; 24-hour creatinine clearance; effective renal plasma flow; glomerular filtration rate

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Changes in renal function can be monitored by following either the glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF) variations. Technetium-99m diethylene triamine pentaacetic acid (DTPA) appears to be the most commonly used agent in the U.S. at present for determining GFR. Many clinicians prefer GFR to evaluate renal function because of their greater familiarity with this measurement. Since the introduction of ^{99m}Tc mercapto acetyl triglycine (MAG3, Mertiatide, Mallinckrodt Medical, Inc., St. Louis, MO) in the U.S. in 1990 as a replacement for ^{131}I OIH (*1,2*), it has gained rapid acceptance as a routine pharmaceutical for the measurement of renal function. Since ERPF agents clear roughly five times as fast as GFR agents, it takes much longer to complete a GFR determination than to measure ERPF by plasma clearance (e.g., 3 hr for single-sample GFR versus 45 min for a single-sample ERPF).

The aim of this study was to arrive at a derived GFR value (dGFR) from ^{99m}Tc MAG3 data, thereby providing an additional clinical parameter of renal function. The advantage of this method is that it uses a 30-min single-radiopharmaceutical protocol to provide both dGFR and ERPF. The results of this protocol were compared to the 24-hr creatinine clearance, the mainstay of quantitative renal function in most institutions.

MATERIALS AND METHODS

Renal examinations were performed in 52 patients with varying degrees of functional impairment. The study consisted of 26 women and 26 men. Their ages ranged from 41 to 85 yr. The ERPF calculations and acquisition parameters have been described in detail elsewhere (*3*). The ERPF results were divided by five to obtain the derived GFR values (dGFR). Within three days of the ^{99m}Tc MAG3 study, each patient had a 24-hr creatinine clearance test, which can provide an estimate of the GFR (*4*) except in cases of severe renal insufficiency (*5*). Creatinine clearance and dGFR values were rounded off to the nearest whole number.

Data analysis are presented as mean +/− standard deviation (s.d.), along with 95% confidence intervals. A two-tailed paired t-test is used to evaluate the difference between dGFR and the creatinine clearance; a simple linear regression was used to plot the data. A value of $p < 0.05$ was considered significant.

RESULTS

The results are listed in Table 1. A plot of the dGFR values and the 24-hr creatinine clearance results is shown in Figure 1, along with the linear regression equation $Y = 0.56 + 1.036 \times X$; $R^2 = 0.94$. The standard error of the estimate (s.e.e.) was 7 ml/min. Additional results of the statistical data analysis are listed in Table 2. The global dGFR values were highly correlated with the 24-hr creatinine clearance, $r = 0.97$, $p < 0.05$.

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TABLE 1
Global GFR Values (ml/min)

Patient	Creatinine clearance	dGFR
1	15	14
2	9	10
3	48	52
4	60	52
5	21	21
6	70	73
7	23	27
8	22	35
9	64	67
10	31	41
11	14	18
12	15	11
13	11	16
14	88	88
15	64	62
16	79	87
17	33	40
18	40	47
19	13	11
20	24	28
21	32	38
22	76	75
23	51	52
24	30	32
25	33	33
26	51	39
27	79	78
28	107	119
29	68	66
30	52	49
31	57	58
32	24	25
33	22	21
34	59	66
35	25	21
36	17	24
37	36	35
38	30	28
39	61	56
40	74	70
41	53	65
42	28	25
43	16	21
44	97	122
45	28	24
46	50	47
47	27	30
48	26	35

There were four cases of acute renal failure, with creatinine clearances of 79, 11, 59 and 11 ml/min. Their dGFRs were 103, 41, 96 and 23 ml/min, respectively. No transplant rejection cases were encountered for assessment.

One patient demonstrated a difference that was four s.d.s from the mean, whereas the other 47 patients were within two s.d.s of the mean. This patient (Patient 44) had a creatinine clearance of 97 and a dGFR of 122 ml/min, for a difference of 25 ml/min. Deletion of that patient from the analysis would result in a smaller s.d. of the difference between both techniques, with dGFR being 1.40 +/− 5.31 units larger on average.

The patient was a 38-yr old man with a history of nephrotic syndrome of unknown cause. The perfusion phase and clearance phase images looked normal. The kidney time activity curves (TAC), the time to peak and the ERPF (right 302, and left 309 ml/min) were normal for the patient's age and gender. The dGFR was also in the normal range.

Nephrotic syndrome is characterized by albuminuria and decreased serum albumin (protein loss) due to degenerative lesions of the renal tubules, and can occur in the acute or chronic setting. Two explanations may be proposed for this patient's results being four s.d.s from the mean. First, the creatinine clearance result could have been in error. The current study did not allow for testing reproducibility. Second, nephrotic syndrome may be an exclusion criterion for this technique. This assumes that in nephrotic syndrome subjects, the GFR decreases more than the ERPF and the dGFR therefore overestimates the creatinine clearance. This hypothesis could be tested in a population larger than that used for the current study. In addition, a larger study would allow for a better definition of selection and exclusion criteria.

DISCUSSION

The practice of clinical renography requires the selection of appropriate techniques and radiopharmaceuticals on the basis of expected pathology for the evaluation of renal function. These choices should maximize the clinical information with minimal or no additional radiation exposure. This is particularly important at a time when nuclear medicine is evolving towards increasing camera and computer sophistication, and many technologists may no longer have adequate training or time to obtain reliable laboratory measurements on plasma samples. In addition, regulations associated with the Clinical Laboratory Improvement Act have added new levels of administrative requirements for laboratories handling body fluids and, therefore, many nuclear medicine departments are reducing the handling of in vitro preparations by introducing innovative techniques (*6–8*). Still others are avoiding this additional administrative burden by eliminating procedures that require blood or urine samples (*9*).

Until the early part of 1990, at our institution it was customary to use ^{99m}Tc DTPA and ^{131}I OIH to obtain the appropriate renograms and to calculate both the GFR and ERPF. With the widespread clinical use of ^{99m}Tc MAG3, the GFR parameter can no longer be calculated by direct measurement. However, there are techniques that allow the calculation of both parameters with the use of an additional radiopharmaceutical. For instance, one could perform a ^{99m}Tc MAG3 study in the morning, and follow 3 hr later with a ^{99m}Tc DTPA study. A second technique uses simultaneous injections of ^{51}Cr ethylene diamine tetraacetate (EDTA) and ^{99m}Tc MAG3 (*10*). Finally, an injection of 1 mCi of ^{99m}Tc DTPA, could be followed by an injection of 10 mCi of ^{99m}Tc MAG3 7 min later (*11*). These

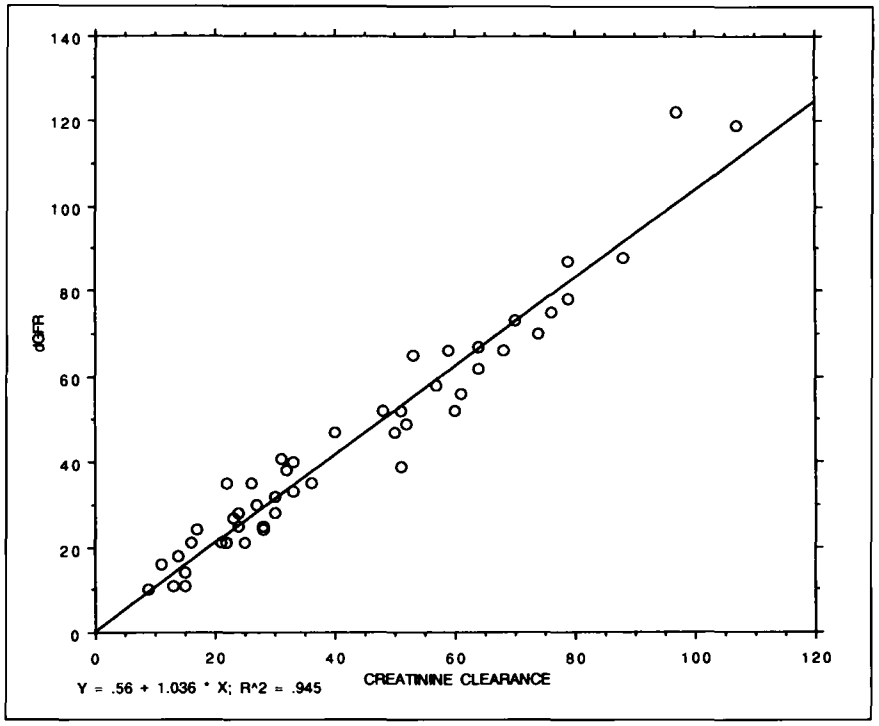

FIGURE 1. Correlation between the GFRs using both techniques.

techniques, however, still require an additional radiopharmaceutical, in vitro preparations of standards, the added burden of handling body fluids, and the extra radiation exposure.

A number of clinicians use ^{99m}Tc MAG3 as a functional substitute for ^{131}I OIH. Others use it as a replacement for ^{99m}Tc DTPA because of its more efficient extraction by the kidney, and its improved target-to-background ratios (*12*). Additionally, in vitro single- and two-plasma techniques, as well as in vivo camera methods for the determination of ERPF, have been developed and adapted for ^{99m}Tc MAG3. They are described in detail in the literature (*13–18*). Clinical procedures, such as urea clearance and the endogenous creatinine clearance have been widely used despite the questions raised regarding what is actually measured by these clearance data (*19*). The 24-hr plasma clearance of creatinine nevertheless remains the mainstay of quantitative renal analysis in most institutions. Plasma creatinine levels alone are principally used in the diagnosis and management of kidney disease when renal function is markedly compromised to approximately 25% of normal (*19*).

GFR, the volume of plasma ultrafiltrate produced per minute by renal glomeruli, is an important renal parameter.

TABLE 2
Student's T-Test Statistics for Paired Data

	Mean	S.D.	95% confidence
Creatinine clearance	42.77	24.81	[35.61, 49.97]
dGFR	44.67	26.64	[36.93, 52.40]
Difference	−1.90*	6.26	[−3.71, −0.08]

* 2-Tailed paired t-test for the difference is $p < 0.05$.

The 24-hr creatinine clearance overestimates GFR in patients with severe renal impairment. This is due to a small element of tubular secretion which becomes more significant as glomerular filtration drops (*20*). Inulin, a fructose polysaccharide, has served as the gold standard for measuring GFR, but the technique is too laborious for routine clinical use (*4*).

GFR has been useful in assessing the fate of the transplanted kidney. The ratio of GFR to ERPF yields the filtration fraction (FF) which has been reported as a clinical tool. When FFs are abnormal, they tend to be high and usually indicate that tubular function is more seriously disrupted than is the glomerular filtration (i.e., GFR values are closer to normal) (*19*). The FF can be a valuable clinical parameter, and it can be measured most easily in a laboratory with facilities for simultaneous determinations of GFR and ERPF. The filtration fraction cannot be calculated using a derived GFR because it is not an independent measurement.

The ERPF is a measure of renal function and can be used, like GFR or the 24-hr creatinine clearance, to evaluate renal disease and monitor changes. Since the normal filtration fraction is 20%, ERPF agents clear from the body about five times as fast as GFR agents. In most chronic renal diseases, the filtration fraction is largely unaffected; the GFR can therefore be calculated by dividing the ERPF by five (*4,20,21–23*).

Our study protocol sought to investigate the possibility of arriving at derived GFR values (dGFR) from ^{99m}Tc MAG3 data. Our results showed good agreement with the values obtained using the 24-hr creatinine clearance, $r = 0.97$, $p < 0.05$.

Study Limitations

The results of this study must be evaluated with caution due to the small patient sample size and the use of strict selection

criteria. Para-aminohippuric acid (PAH) is the gold standard as a reference compound for measurement of ERPF, however, it is not well suited for routine studies. Iodine-131 OIH has similar biological properties to PAH, and although its clearance values are 15% lower than PAH, it has been used extensively. Regression equations have been used correlating the ^{99m}Tc MAG3 clearance to a corresponding OIH values because of the pharmacokinetic differences that exist between both agents (*2,22,24*). In this type of study, one can derive a value that closely resembles actual GFR measurement. This is because we are using a tubular agent (^{99m}Tc MAG3) which has only a small component (not more than about 2%) that is cleared by glomerular filtration (*23*).

Secondly, the estimation of dGFR with this procedure may not be accurate in patients with acute renal failure or those with transplant rejection, since the GFR in these instances typically decreases more than does the ERPF. These particular limitations, however, can be clearly identified in the ^{99m}Tc MAG3 study by noting prolonged parenchymal transit or retention of the radiopharmaceutical on the images (*23*).

Third, the dGFR and creatinine clearance GFR are not interchangeable in all situations. The reader is cautioned that the dGFR cannot be used to define differences in glomerular filtration between ACE-inhibited and non-ACE-inhibited studies. ERPF does not drop, as does true GFR, following ACEI in patients with renin-mediated hypertention caused by renal artery stenosis (RAS). Using the ERPF to predict GFR in these patients could result in a false negative diagnosis for RAS.

Finally, when the ERPF values are below approximately 125 ml/min, the percentage of error in the measurement may be large and hence the dGFR may be inaccurate even though it still may indicate correctly that the function is impaired (*23*).

CONCLUSION

Our present study investigated the possibility of arriving at dGFR values from ^{99m}Tc MAG3 data. The results of our initial work suggests that this is a useful, convenient and reliable method for assessing GFR, assuming that accurate patient selection criteria are used. The technique will require additional testing in a larger population to further define its usefulness, accuracy, technical limitations and the associated selection/exclusion criteria.

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REFERENCES

1. Fritzberg AR, Kasina S, Eshima D, et al. Synthesis and biological evaluation of technetium-99m MAG3 as a hippuran replacement. *J Nucl Med* 1986;27: 111–116.
2. Eshima D, Taylor A Jr. Technetium-99m mercaptoacetyltriglycine: update on the new ^{99m}Tc renal tubular function agent. *Seminars Nucl Med* 1992;22: 61–73.
3. Arroyo AJ. Effective renal plasma flow determination using technetium-99m MAG3: comparison of two camera techniques with the tauxe method. *J Nucl Med Technol* 1993;21:162–166.
4. Taylor A Jr, Datz, FL. *Clinical practice of nuclear medicine*. New York, NY: Churchill Livingstone; 1991:124–142.
5. Goates JJ, Morton KA, Whooten WW, et al. Comparison of methods for calculating glomerular filtration rate: technetium-99m-DTPA scintigraphic analysis, protein-free and whole-plasma clearance of technetium-99m-DTPA and iodine-125-iothalamate clearance. *J Nucl Med* 1990;31:424–429.
6. Mrhac L, Zakko S, Salih O. Is it possible to avoid standards in studies with blood samples? *J Nucl Med Technol* 1995;23:271–274.
7. Allen EW, Leonard JC, Ficken VJ. Simplified Tc-99m MAG3 ERPF determination not requiring the counting of a Tc-99m standard [Abstract]. *J Nucl Med* 1992;33:1034.
8. Arroyo AJ, Rakowski JT. Single-sample effective renal plasma flow determination with Tc-99m-MAG3, not requiring a standard. *J Nucl Med Technol* 1994;22:218–221.
9. Taylor A Jr, Nally VJ. Clinical applications of renal scintigraphy. *AJR* 1995;164:31–41.
10. Fresco GF, DiGiorgio F, Curti GL. Simultaneous estimation of glomerular filtration rate and renal plasma flow. *J Nucl Med* 1995;36:1701–1706.
11. Carpenter S, Caride VJ. Routine renal scintigraphy with sequential injections of Tc-99m DTPA and Tc-99m MAG3. *J Nucl Med Technol* 1994;22: 213–217.
12. Taylor A Jr, Eshima D, Christian PE, et al. Technetium-99m MAG3 kit formulation: preliminary results in normal volunteers and patients with renal failure. *J Nucl Med* 1988;29:616–622.
13. Russell CD, Thorstad BL, Yester MV, et al. Quantitation of renal function with technetium-99m MAG3. *J Nucl Med* 1988;29:1931–1933.
14. Taylor A Jr, Corrigan P, Eshima D, et al. Prospective validation of a single-sample technique to determine technetium-99m MAG3 clearance. *J Nucl Med* 1992;33:1620–1622.
15. Fine EJ, Axelrod M, Gorkin J, et al. Measurement of effective renal plasma flow: a comparison of methods. *J Nucl Med* 1987;28:1393–1400.
16. Russell CD, Taylor A Jr, Eshima D. Estimation of technetium-99m MAG3 plasma clearance in adults from one or two blood samples. *J Nucl Med* 1989;30:1955–1959.
17. Taylor A Jr, Halkar RK, Garcia E, et al. A camera-based method to calculate Tc-99m MAG3 clearance [Abstract]. *J Nucl Med* 1991;32:953.
18. Taylor A Jr, Garcia E, Jones M, et al. An optimized camera-based method to calculate Tc-99m MAG3 clearance [Abstract]. *J Nucl Med* 1992;33:953.
19. Tauxe WN, Dubovsky EV. *Nuclear medicine in clinical urology and nephrology*. Norwalk, CT: Appleton-Century-Crofts; 1985:70–72.
20. Russell CD, Dubovsky EV. Measurement of renal function with radionuclides. *J Nucl Med* 1989;30:2053–2057.
21. Muller-Suur R. Radiopharmaceuticals: their intrarenal handling and localization. In: Murray IPC, Ell PJ. *Nuclear medicine in clinical diagnosis and treatment. Volume I*. New York, NY: Churchill Livingstone; 1994:202.
22. Bubeck B, Brandau W, Weber E, et al. Pharmacokinetics of technetium-99m-MAG3 in humans. *J Nucl Med* 1990;31:1285–1293.
23. Russell CD, Young D, Billingsley JD, et al. Technical procedures for use of the new kidney agent technetium-99m MAG3™. *J Nucl Med Technol* 1991; 19:147–152.
24. Chervu LR, Blaufox MD. Renal radiopharmaceuticals: an update. *Seminars Nucl Med* 1982;12:224–245.